REMARKS

Specification

By the present amendment, Applicants have deleted the previous priority claim and have inserted in its place, paragraph [0001.1]. Applicants hereby cancel their claim to the priorities of U.S. application no. 09/835,243; U.S. application No. 09/606,909; and U.S. application no. 09/417,671 . Upon entry of the amendment, Applicants submit that the priority claim will recite that the instant application is a continuation-in-part of U.S. application no. 09/843,746, filed June 29, 2001.

Claims

By the present amendment, claims 69 and 85 have been amended to clarify that the reduction in dose for intradermal delivery is to achieve the systemic bioavailability achieved when the non-reduced dose is administered subcutaneously. In response to the Examiner's comments (*see*, Office Action, mailed December 7, 2006, at page 7) the comparison of systemic bioavailability achieved with the reduced dose delivered intradermally as compared to the systemic bioavailability achieved with the full dose delivered subcutaneously is a relative one. New claims 106 and 107 specify the different means by which the systemic bioavailability may be measured. The amendments to claims 69 and 85 and new claims 106 and 107 are fully supported by the specification, *see, e.g.*, Examples I through VIII of the instant specification. By the present amendment, claims 74 and 94 have been amended to correct typographical errors. Claim 88 has been amended for purposes of clarity. Claim 88 has been amended to recite that the microneedle has an outlet with an exposed height between 0 and 1 mm. Support for the recitation can be found, for example, at p. 17, *ll.* 6-7. New claim 105 has been added to specify specific embodiments of the method recited in claim 85 wherein delivery of the substance occurs at a depth between 0.3 to 2.0 mm. Support for claim 105 can be found, for example, at page 6, *l.* 30 – p. 7, *l.* 4. No new matter has been added.

Claims 69-75, 77-95, and 97-105 are pending.

I. THE CLAIMS ARE PATENTABLE OVER U.S. PATENT NO. 5,527,288 TO GROSS *ET AL.* IN VIEW OF U.S. PATENT NO. 6,007,821 TO SRIVASTAVA *ET AL.*

Claims 69-75, 77-89, 93-95 and 97-104 are rejected over U.S. Patent No. 5,527,288 to Gross *et al.* (Gross) in view of U.S. Patent No. 6,007,821 to Srivastava *et al.* (Srivastava).

Specifically, the Examiner contends that Gross teaches an intradermal compartment drug delivery device. According to the Examiner, it is inherent that the needle have at least an exposed height of 0 mm. The Examiner concedes that Gross fails to disclose that a substance can be administered at a reduced dose (10-30%) to achieve the same level of systemic bioavailability as compared to subcutaneous administration. However, the Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than subcutaneous injections in a method for treating autoimmune diseases. The Examiner concludes that it would have been obvious to use the invention of Gross to administer the composition at a reduced intradermal dosage as taught by Srivastava. For the following reasons, Applicants respectfully disagree.

A. Instant Claims 69-75 and 77-84

Instant claims 69-75 and 77-84 recite a method for delivering a substance into an intradermal compartment of a human subject's skin comprising:

(a) administering a substance through at least one small gauge hollow needle having an outlet with an exposed height between 0 and 1 mm;

(b) said outlet being inserted into the skin to a depth of between 0.3 and 2 mm, such that delivery occurs between 0.3 and 2 mm;

(c) wherein a dosage of the substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to the dose required to achieve the systemic bioavailability when the substance is delivered to a subcutaneous compartment of the human subject's skin.

The Examiner relies on Gross to provide the teaching or suggestion of claim elements (a) and (b); and relies on Srivastava to provide the claim element (c). However, the cited references are completely silent as to the needle configuration and needle placement as required by elements (a) and (b). Moreover, the references are equally silent as to a dosage of the substance for achieving systemic bioavailability of the substance being reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin. Thus, for the reasons discussed below, the cited references fail to render obvious the claimed invention.

First, Gross does not describe the insertion of a needle so that *both* its outlet depth and exposed height of the outlet are located within the intradermal compartment of the subject's skin. Further, Gross does not describe a needle having an outlet with an exposed height of

about 0 to 1 mm. These elements of the claims are not taught or suggested by Gross. Second, Gross proposes methods and devices that *non-selectively* administer drugs below the epidermis, *i.e.*, to the interface between the epidermis and the dermis, or to the interior of the dermis or subcutaneously (*see* Gross at col. 3, *ll.* 46-49). Furthermore, Gross is silent as to the dosage of the substance for achieving systemic bioavailability of the substance being reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin, nor is it the inevitable result of practicing Gross.

Indeed, accurate delivery of a substance to the intradermal compartment, including accurate needle placement and the use of a needle with correct outlet depth in accordance with the claimed method has a very different outcome as compared to delivery in accordance with Gross as demonstrated by the concurrently filed Declaration under § 1.132 of Dr. Ronald J. Pettis ("Declaration"). The Declaration demonstrates that delivery in accordance with the claimed configuration has a dramatic effect on the results obtained when compared to the results reported by Gross. Namely, administration in accordance with the claimed configuration dramatically affects the resulting pharmacodynamic profile, including both the rate and magnitude of the drop in blood glucose concentration as compared to Gross. *See*, Declaration.

As reported in Example 1 of Gross, when insulin was administered "intradermally" to rabbits, the rabbits' glucose levels dropped, and rose again when insulin administration ceased. However, rabbits receiving insulin in accordance with the claimed method demonstrated a much more precipitous drop in blood glucose concentrations. *See*, Declaration at ¶ 15 and Exhibits B, C, D, and E. In fact, as a result of intradermal administration of insulin in accordance via the claimed method at 100 IU/mL, the blood glucose concentrations of the test animals dropped to levels which could not be reversed by ceasing administration of insulin, nor by intervening through administration of glucose to the hypoglycemic test animals. This result indicates that there was an improved bioavailability of insulin when administered via the claimed method; hence the same hypoglycemic shock experienced by the test animals, as opposed to the methodology described in Gross, where the animals easily recovered once insulin administration ceased. Had Gross been practicing intradermal delivery as claimed in the instant application, the same result would have been observed; it was not. *See*, Declaration at ¶ 8.

One possible explanation for the differences in the observed pharmacodynamic response is that Gross fails to define the intradermal compartment, but merely describes

delivery below the epidermal layer of the skin. Further, Gross is devoid of any teaching relating to the configuration of the needle required to prevent leakage of the drug substance outside the intradermal space. It is the Applicants' disclosure, not Gross's, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. *See*, specification at p. 16, *l.* 24-p. 17, *l.* 12. Unless the skin seals around the needle, the drug substance will effuse out of the skin due to backpressure exerted by the skin itself, or the pressure built up from the accumulating fluid. The Applicants' specification sets forth principles and parameters relating to length of the needle and configuration of its outlet to prevent unwanted leakage. *See*, instant specification at p. 16, *l.* 24-p. 17, *l.* 12. In particular, the specification describes the use of needles that have *both* a length sufficient to penetrate the intradermal space *and* an *outlet depth within the penetration space* to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure. *See*, instant specification at p. 16, *l.* 25-p. 17, *l.* 6. Gross neither appreciates nor addresses the significance of these parameters for practicing the claimed method. Srivastava fails to remedy this deficiency.

Contrary to the Examiner's contention, it is not inherent that the needle disclosed in Gross has an exposed height of at least 0 mm. The instant specification specifies that a needle outlet with an exposed height of 0 mm *has no bevel and is at the tip of the needle*. *See*, instant specification at p. 17, *ll.* 16-17. There is simply no teaching or suggestion of such a needle outlet in Gross, nor does Srivastava remedy this deficiency.

In contrast to the Examiner's contention, Srivastava fails to teach or suggest achieving a systemic bioavailability of a substance with an intradermal dosage that is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin. The disclosure of Srivastava relates to treatment of autoimmune diseases using complexes of heat shock/stress protein (hsps) to suppress the immune response. Srivastava monitors the efficacy of the treatment, not by detecting the systemic bioavailability of substance, but instead by detecting "... on the level of the molecular and cellular agents involved in the immune response *(e.g.*, cytotoxic T-cells), or on the level of secondary symptoms." *See*, Srivastava at col. 23, *ll.* 53-58. Srivastava thus fails to teach or suggest a pharmacokinetic measure of efficacy, such as the instantly claimed systemic bioavailability.

Furthermore, Srivastava's methods for treating an autoimmune disease in a subject are based on hsp immunotherapeutic agents which mediate a *local, cellular response*, rather than achieve a systemic effect (*see*, col. 5, *l.* 62 to col. 6, *l.* 13). Thus, when Srivastava discloses that intradermal injections require a lower dosage than subcutaneous dosages, it does *not* follow that intradermal injections achieve a higher systemic bioavailability of the injected substance (*i.e.*, complexes of hsps) as compared to delivery of the substance to the subcutaneous compartment of the skin. Accordingly, Srivastava fails to describe or suggest that a dosage of the substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the subject's skin as required by the claims.

In sum, none of the references taken alone or in combination describe or suggest administration via a needle having the claimed configuration and placement in the intradermal compartment. The references taken alone or in combination are equally silent as to an intradermal dosage of a substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the subject's skin. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

B. Instant Claims 84-95 and 97-104

Instant claims 84-95 and 97-104 recite a method for delivering a substance into an intradermal compartment of a human subject's skin comprising:

(a) injecting or infusing the substance intradermally through one or more microneedles having a length sufficient to penetrate the intradermal compartment and an outlet at a depth within the intradermal compartment;

(b) wherein a dosage of the substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to the dose required to achieve the systemic bioavailability when the substance is delivered to a subcutaneous compartment of the human subject's skin

The Examiner relies on Gross to provide the teaching or suggestion of claim element (a); and relies on Srivastava to provide the claim element (b). However, the cited references are completely silent as to the needle configuration and needle placement as required by element (a). Moreover, the references are equally silent as to a dosage of the substance for achieving systemic bioavailability of the substance being reduced by at least 10% compared

to when the substance is delivered to a subcutaneous compartment of the human subject's skin as required by element (b). Thus, for the reasons discussed below, the cited references fail to render obvious the claimed invention.

First, as described above, Gross does not describe injection or infusion through a microneedle so that *both* the microneedle's outlet depth and exposed height of its outlet are located within the intradermal compartment of the subject's skin. Further, as explained above, Gross proposes methods and devices that non-selectively administer drugs below the epidermis. Furthermore, Gross is silent as to the claimed reduced intradermal dosage of the substance as compared to the subcutaneous dosage of the substance, nor is it the inevitable result of practicing Gross.

As set forth above and in the results of the Declaration, accurate delivery of a substance to the intradermal compartment, including accurate needle placement and the use of a needle with correct outlet depth in accordance with the claimed method has a very different outcome as compared to delivery in accordance with Gross as demonstrated by the results. Rabbits receiving insulin in accordance with the claimed method demonstrated a much more precipitous drop in blood glucose concentrations than reported in Gross. *See*, Declaration at ¶ 15 and Exhibits B, C, D, and E. If Gross had been practicing intradermal delivery as claimed in the instant application, the same result would have been observed; it was not. *See*, Declaration at ¶ 8. The Declaration demonstrates that delivery in accordance with the claimed configuration has a dramatic effect on the blood glucose concentrations in the rabbits administered insulin in this study and the rabbits described in Gross. *See*, Declaration. Srivastava also fails to teach or suggest the claimed features.

Furthermore, as set forth above, Srivastava fails to teach or suggest achieving a systemic bioavailability of a substance with an intradermal dosage that is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the human subject's skin. The disclosure of Srivastava relates to treatment of autoimmune diseases using complexes of heat shock/stress protein (hsps) to suppress the immune response. Srivastava fails to monitor the efficacy of the treatment by detecting the systemic bioavailability of substance. Srivastava thus fails to teach or suggest a pharmacokinetic measure of efficacy, such as the instantly claimed systemic bioavailability.

Furthermore, Srivastava's methods for treating an autoimmune disease in a subject are based on hsp immunotherapeutic agents which mediate a *local, cellular response*, rather than achieve a systemic effect (*see*, col. 5, *l.* 62 to col. 6, *l.* 13). Thus, when Srivastava discloses

that intradermal injections require a lower dosage than subcutaneous dosages, it does *not* follow that intradermal injections achieve a higher systemic bioavailability of the injected substance (*i.e.*, complexes of hsps) as compared to delivery of the substance to the subcutaneous compartment of the skin. Accordingly, Srivastava fails to describe or suggest that a dosage of the substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the subject's skin as required by the claims.

In sum, none of the references taken alone or in combination describe or suggest administration via a microneedle having the claimed configuration and placement in the intradermal compartment. The references taken alone or in combination are equally silent as to an intradermal dosage of a substance for achieving a systemic bioavailability of the substance is reduced by at least 10% compared to when the substance is delivered to a subcutaneous compartment of the subject's skin. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Additionally, it should be noted that in contrast to the Examiner's contention that Applicants provide no quantitative or relative measure for the term "bioavailability" (*see* page 7, lines 1-2 of the Office Action), Applicants respectfully note that a person of ordinary skill in the art could readily determine this pharmacokinetic parameter. The bioavailability of a drug may be simply assessed quantitatively by quantitating the area under the serum concentration curve (AUC), which is a measure of bioavailability. (Exhibit 1, The Merck Manual of Diagnosis and Therapy, 1999, Seventeenth edition, Beers and Berkow, ed., Merck Research Laboratories, Division of Merck & Co., Inc. Whitehouse Station, N.J. (pages 2559-2562).

II. THE CLAIMS ARE PATENTABLE OVER U.S. PATENT NO. 5,250,023 TO LEE *ET AL.* IN VIEW OF U.S. PATENT NO. 6,007,821 TO SRIVASTAVA *ET AL.*

Claims 69-75, 77-89, 90-95 and 97-104 are rejected over U.S. Patent No. 5,250,023 to Lee *et al.* (Lee) in view of U.S. Patent No. 6,007,821 to Srivastava *et al.* (Srivastava). Specifically, the Examiner contends that Lee teaches the intradermal compartment drug delivery device that administers a substance through a hollow needle array and notes the devices shown in Figures 1 and 2. According to the Examiner, it is inherent that the needle have at least an exposed height of 0 mm because delivery of a substance *through* a needle requires that a needle have at least a non-beveled opening that results in an exposed height of

0 mm. The Examiner concedes that Lee fails to disclose that the dosage for the substance for achieving systemic bioavailability is reduced by 10-30% when administered to the intradermal compartment as compared to when the substance is delivered to the subcutaneous compartment. However, the Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than subcutaneous injections in a method for treating autoimmune diseases. The Examiner concludes that it would have been obvious to use the invention of Lee to administer the composition at a reduced intradermal dosage value as taught by Srivastava. For the following reasons, Applicants respectfully disagree.

The rejection is improper because Lee, in fact, does not disclose a method or device for delivering a substance into an intradermal compartment of a human subject's skin, wherein a substance is administered *through* a hollow needle or microneedle as specified by the claims. The claims also specify that the needle's or microneedle's outlet is positioned at a specified depth within the skin. Claims 69-75 and 77-84 specify that the substance be administered through a small gauge hollow needle, having an outlet with a specified exposed height at a specified depth such that delivery of the substance occurs at a specified depth. Claims 85-104 specify that the substance is injected or infused *through* one or more microneedles, having a length sufficient to penetrate the intradermal compartment and an outlet at a depth within the intradermal compartment.

The disclosure of Lee as a whole makes apparent that the methods disclosed therein fail to rely on delivering a substance *through* a hollow needle or microneedle as the claimed methods require. Instead, Lee discloses that the needles form pathways through the skin. See, *e.g.*, the Abstract; col. 5, *ll.* 36-39; col. 5, *ll.* 44-50; and col. 6, *ll.* 32-38.

Both devices disclosed in Lee, an integration-type device and a separation-type device, clearly do not rely on delivery of a substance *through* a hollow needle or microneedle for administration into the skin. For instance, in describing the administration of a hydrophilic drug using the integration-type device (shown in Figure 1), Lee discloses that "the pa[th]way formed by skin needle[](**4**) is temporarily closed by the swelling of skin" in the absence of applying an electrical current to the pathway formed by a skin needle. *See* col. 5, *ll.* 44-50. Application of electrical current is said to cause contraction of the skin and open the pathway of the epidermis layer. *See,* col. 5, *ll.* 51-57. The phenomena described in Lee is inconsistent with a method in which a substance is actually delivered through a hollow needle or microneedle as the claimed methods require, where any skin swelling would fail to prevent delivery through a lumen of a steel needle.

Similarly, Lee's method for administering a substance from a separation-type device (shown in Figure 2) clearly does not rely on delivery through hollow needles or microneedles. In connection with using the separation-type device, Lee discloses "[l]ightly compressing a skin needle plate[](**15**) on the skin, and forming the drug delivery pathway on skin, and removing the skin needle plate(**15**), and on that skin, compressing the patch body[](**30**) ...." Col. 6, *ll.* 33-37. In other words, the needles are not in the skin at the time when the drug is actually delivered.[1] Thus, the separation-type device in Lee does not rely on delivering drug through hollow needles or microneedles.

Accordingly, Lee does not teach or suggest delivering a substance through a hollow needle or microneedle, let alone teach or suggest delivering a substance with the configurations recited by claims 69 and 85 and their dependent claims. Srivastava does not remedy these deficiencies as it fails to teach or suggest the depth in which a needle outlet is positioned within the skin. Thus, since the references fail to teach or suggest all of the claim limitations, Applicants submit that the rejection has failed to set forth a *prima facie* case of obviousness.

Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the amendments and remarks made herein now place the application in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosures

[1] Moreover, Applicants note that Lee teaches that the use of skin needles can be avoided altogether by using an electric razor to alleviate the resistance of the epidermis layer. Col. 6, *ll.* 40-45.